PATENT APPLICATION

IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicants: Alice C. MARTINO et al

For: TABLET FORMULATION

Serial No.: 09/656 364 Group: 1617

Confirmation No.: 3730

Filed: September 6, 2000 Examiner: Sharareh

Atty. Docket No.: Pharmacia Case 6107.N CN2

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR 1.132

I, Alice C. Martino, declare:

THAT, I received a B.S. degree in Pharmacy from Purdue University in 1980;

THAT, I received a Ph.D. degree in Pharmaceutics from The University of Iowa in 1987;

THAT, I worked at G.D. Searle as an Industrial Pharmacist prior to graduate school from 1980 to 1982;

THAT, I worked at Burroughs Wellcome as a Pharmacy Intern in 1979;

THAT, I worked at Oquawka Professional Pharmacy as a Pharmacist from 1983 to 1986;

THAT, I worked at Walgreens as a Pharmacist and Pharmacy Intern from 1981 to 1982 and 1976 to 1977;

THAT, I worked at Keefer's Pharmacy as a Pharmacy Intern from 1976-1979;

THAT, I joined The Upjohn Company in 1987 as a Research Scientist;

THAT, I am the author or co-author of about eight external scientific publications, about three of which deal with delavirdine (RESCRIPTOR Tablet) formulation and product development;

THAT, I am the inventor or co-inventor of about six U.S. Patent applications and one U.S. Patent;

THAT, my present position with Pharmacia is Principal Research Scientist and my daily duties and responsibilities include design and execution of pharmaceutical formulation development from inception to product launch, including novel exploratory formulations, formulation advisor and leader of a formulation team;

THAT, being so qualified the declarant further states;

THAT, I am a co-inventor of the above-identified patent application.

STANDARD FOR ASCERTAINING THE SCOPE OF THE INVENTION

THAT, while the Examiner's action centers on the definition of "poorly soluble", "fairly soluble", "highly soluble" and "rapidly precipitating", the most important aspect to be clearly understood is that the active pharmaceutical ingredient encompassed in the invention are those for which the fairly or highly soluble compound is *higher* in solubility compared to its relatively *poorly* soluble free base or free acid. For this reason, Remington definitions were not specifically used in this application so that, hopefully, the case could be most clearly understood;

THAT, Remington solubility ranking can be used to visualize or better explain the case;

THAT, page 3, lines 10-20, of the above-identified patent application, provides the clear quantitation in terms of relative solubility, that is, the more soluble compound (typically a salt of the type used to *increase* solubility). Specifically, in the preferred case which is prone to most critical precipitation, the solubility of the higher soluble compound (for example a salt), would be roughly at least 100 times more soluble than its parent free base or free acid. As a consequence, thereto, greater than ninety percent (90%) of a drug meeting these criteria precipitate within the timeframe as described in the application (See Figure 1 of Exhibit 1 that is appended to and made a part of this Declaration);

09/656 364

THAT, to select and apply the Remington definitions, as an example, a sparingly soluble salt [10-30 mg/ml] is still at least 10-fold higher in solubility than either its very slightly soluble [0.1-1 mg/ml] or its practically insoluble [<0.1 mf/ml] free acid or base moiety. Likewise, in another example, a freely soluble compound as defined by Remington [100-1,000 mg/ml] is greater than 10-fold higher in solubility than its slightly soluble [1-10 mg/ml] free acid or base moiety;

THAT, a comparison of the aqueous drug solubility as a function of time of the active pharmaceutical ingredient (API) representative of those encompassed in the claims of the above-identified application and the APIs representative of those not encompassed in the claims of the above-identified application are shown in Figure 2 of Exhibit 1;

THAT, the profile of the drug solubility of the APIs encompassed by the claims of the above-identified application reach a higher value (percent drug in solution) as depicted by the top line in Figure 2;

THAT, the profile of the drug solubility of APIs not encompassed by the claims of the above-identified application would mimic the Fuchsia profile depicted by the bottom line in Figure 2;

THAT, in specific cases, some may choose to produce salts which are less soluble than the parent free base/free acid, for reasons such as sustained release, formulation delivery system, taste masking or to increase deposition into more lipophilic membranes. In those cases the shape of their drug solubility profile would mimic the Fuchsia profile shown in Figure 2, although the timescale may be altered;

THAT, the Fuschia profile is consistent for salts or anhydrous forms which are less than or equivalently soluble to the parent compound and also with, for example, a parent free base compound or ancther compound capable of forming a hydrate;

09/656 364

THAT, salts prepared using counter ions which typically do not increase solubility, such as calcium or long chain aliphatic acid or base salts, are a couple of examples. Therefore, not all salts that one skilled in the art might decide to produce are usable in the formulation claimed in the above-identified application. For example, in Akkerboom et al (U.S. Patent 5 211 958) it can be surmised that the authors apparently deliberately produced a relative insoluble calcium salt of chlortetracycline in an attempt to reduce solubility and thereby reduce their drug taste problem.

ANTICIPATION BY AKKERBOOM ET AL U.S. PATENT 5 211 958

THAT, I have reviewed U.S. Patent 5 211 858 that was granted to Akkerboom et al;

THAT, Akkerboom et al does not disclose a tablet that contains a rapidly precipitating drug as is required in the tablet compositions of the above identified application.

THAT, a hydrate is not a salt of a compound but it is the compound itself, which has retained water of crystallization. See Exhibit 2 - Concise Chemical and Technical Dictionary, 1974, p 553, which is appended to and made a part of this Declaration,

THAT, hydrates of tetracycline, doxycycline, oxytetracycline and chlortetracycline are not salts and therefore are not more soluble salts of a poorly soluble acidic or basic drug or a more soluble anhydrous form of a poorly soluble drug. Furthermore, and more important, none of these hydrated drugs can generate a supersaturated solution in water or physiological fluids at body temperature;

THAT, the calcium salt of chlortetracycline, referred to in Akkerboom et al as a salt, is a chelate, a complex compound in which the calcium ion is sequestered and firmly bound into the tetracycline ring (See Exhibit 3 - Dorland's Illustrated Medical Dictionary, Twenty Sixth Edition, 1981, p 252, which is appended to and made a part of this Declaration). Thus, it

09/656,364

is this Declarant's opinion that calcium chlortetracycline is neither a more soluble salt of chlortetracycline nor a more soluble anhydrous form of chlortetracycline. Furthermore, calcium chlortetracycline cannot generate a supersaturated solution in water or physiological fluids at body temperature;

THAT, the invention in the above-identified application is a tablet formulation that produces a super saturated state, i.e. a higher solution concentration of a drug in solution, upon *in vivo* dissolution of a tablet that is prepared with soluble salts of poorly soluble free acids or free bases or anhydrous forms of hydratable free acids or free bases and this resulting supersaturated state is maintained by means of a binder, such as HPMC. The advantage of the supersaturated state is that the higher drug concentration in solution in the GI tract results in faster absorption and improved oral bioavailability.

UNOBVIOUSNESS OVER WEINTRAUB ET AL U.S. PATENT 4 013 785

THAT, I have reviewed U.S. Patent 4 013 785 that was granted to Weintraub et al;

THAT, Weintraub et al discloses a tablet that requires the presence of n-acetyl-p-aminophenol (APAP) and that can contain "other pharmaceutically active ingredients". Some of the other pharmaceutically active ingredients that they refer to can be in the form of a rapidly precipitating drug. However, they do not teach or suggest how much of the other pharmaceutically active ingredient can be included in the tablet, let alone the 5% to 60% required in the tablet compositions of the above referred to application. Furthermore, the tablet described in the above identified application contains a rapidly precipitating drug as the only active pharmaceutical ingredient. The tablet described in Weintraub, et al, must contain APAP as an active ingredient and APAP is not a rapidly precipitating drug. Furthermore,

the tablet described in Weintraub, et al, requires use of solvent, heating/drying, and/or milling, and none of these processes are required in the above identified application.

THAT, one skilled in the art would not be led by the teaching of Weintraub et al to utilize the amount of rapidly precipitating drug required in the tablet composition of the above identified application.

CONCLUSIONS

THAT, the terms "poorly soluble", "fairly soluble" and "highly soluble", do not render the claim of the above-identified application indefinite to one skilled in the art because these are relative terms that are used only to show that the salts utilized in the tablet formulation of the above identified invention are more soluble (i.e., "fairly soluble" or "highly soluble") than the hydrated parent free acid or free base ("poorly soluble"). The specification makes it clear (1) that the "fairly soluble" and "highly soluble" compounds generate a supersaturated solution when introduced into water, or simulated physiological fluids at room temperature, whereas "poorly soluble" compounds do not and (2) that 90% of the "fairly soluble" and "highly soluble" compounds precipitate out of solution within 60 minutes in the absence of HPMC or other binder.

THAT, tetracycline hydrates as utilized in the Akkerboom et al tablet are neither (a), more soluble salts of poorly soluble acidic or basic drugs nor (b), anhydrous forms of poorly soluble acidic or basic drugs. It is impossible for a tetracycline hydrate to form a supersaturated state upon contact with water. Furthermore, calcium tetracycline is reported to be less soluble than tetracycline at pH 6.2-6.8, the pH of the intestine and, therefore, it is impossible for calcium tetracycline to generate a supersaturated state in the intestine and likewise, calcium chlortetracycline as utilized in the Akkerboom tablet is also probably not capable of

09/656 364

generating a supersaturated state. Therefore, the Akkerboom et al compositions should not be capable of enhancing the oral absorption since the hydrates of tetracycline, oxytetracycline and chlortetracycline as well as calcium chlortetracycline cannot generate a supersaturated state.

THAT, Weintraub et al, U.S. Patent 4 013 785, is directed to a tablet in which the primary active ingredient is APAP, which is not a rapidly precipitating drug because it is neither a salt of a poorly soluble drug nor an anhydrous form of a hydratable free acid or base drug and therefore it cannot generate a supersaturated state on contact with water. They neither teach nor suggest how much of the "other pharmaceutically active drug" that they refer to should be contained in their tablet. Also, the Weintraub, et al, tablet requires the presence of APAP whereas the tablet formulation described in the above identified application does not contain APAP.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: 21 November 2002 Alice C. Martino

Alice C. Martino

091656 364

EXHIBIT 1

General case for rapidly precipitating drug:

API or API salt + H20 → dissolve then in <60 min (Or physiological fluids) 1) ↓ppt. to non-therapeutic amount of API

Preferred/most probable case:

API or API salt + H20 → dissolve then in <60 min 1) ↓ppt. at > 90%

2) inadeq. Drug <10% left for drug response

Preferred API, either:

a) Fairly or highly soluble salt RELATIVE TO its poorly soluble free base/acid

b) Anhydrous form of poorly soluble free base or acid

FIG. 1

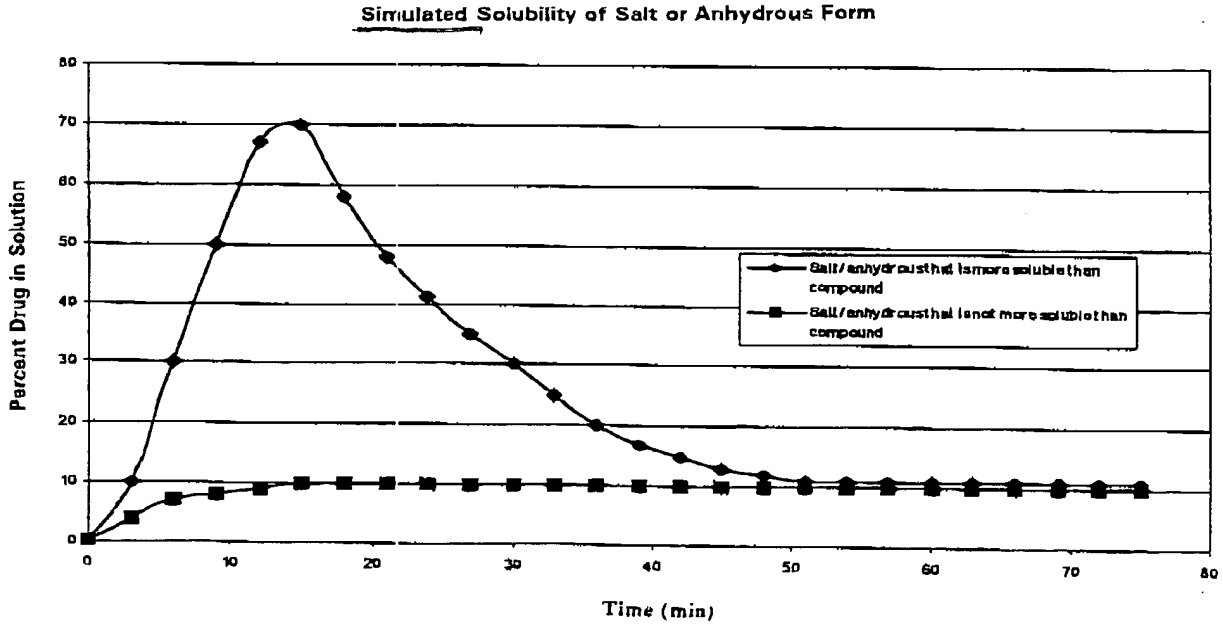

FIG. 2

09/654,864

EXHIBIT 2

Third Enlarged Edition

CONCISE CHEMICAL and TECHNICAL DICTIONARY

Edited by
H. Bennett, F.A.I.C.
B. R. Laboratory
Miami Beach, Florida, 33140, U. S. A.

1 9 7 4
CHEMICAL PUBLISHING CO., INC.
200 Park Avenue South New York, N. Y. 10003

Concise Chemical and Technical Dictionary, 1974, p 553

09/656364

hydrangea (seven barks). Dried root of Hydrangea arborescens containing hydrangin, saponin; used in medicine.

hydrangin. $C_{36}H_{28}O_{11}$; m.w. 609.2; wh. need.; m.p. 228-235; i.w.; s.eth.; s.chl.; glucoside.

"Hydraphtal" GF, GB. soap and solvent naphtha.

Hydraprint. clay.

hydrargillite. See gibbsite.

hydrargyri succinimidium. See Hydrargol.

hydrargyrum. Latin name for mercury; used in medicine, pharmacy.

hydrase. Enzyme that adds water to its substrate without causing a split.

Hydrasolv. pine oil.

hydrastine. $C_{21}H_{21}NO_6$; m.w. 383.17; col. rhomb. pr.; m.p. 132; i.w.; s.bz.; s.chl.; alkaloid.

***l*-β-hydrastine.** $C_{21}H_{21}NO_6$; m.w. 383.39; orth.pr.f.al.; m.p. 132; i.w.; s.chl.; s.acet.

hydrastine bitartrate. $C_{21}H_{21}O_6N.C_4H_6O_6.4H_2O$; m.w. 605.28; wh. cr.; s.h.w.

hydrastine hydrochloride. $C_{21}H_{21}NO_6.HCl$; m.w. 419.64; wh. powd., hyg.; m.p. 116; s.w.; s.al.; used in medicine.

hydrastine sulfate. $(C_{21}H_{21}O_6N)_2.H_2SO_4$; m.w. 864.42; ylsh. powd., hyg.; s.w.; s.al.; used in medicine.

hydrastinine. $C_{11}H_{13}NO_3$; m.w. 207.11; wh.-ylsh. need. f. lgr.; m.p. 116; s.h.w.; s.al.; used in alkaloid.

hydrastinine bisulfate. $C_{11}H_{11}NO_2.H_2SO_4$; m.w. 287.17; gr. fluores. cr.; s.w.; s.al.

***i*-hydrastinine hydrochloride.** $C_{11}H_{11}NO_2.HCl$; m.w. 225.56; yel. need.; aq. sol. bl. fluoresc.; s.w.; s.al.; used in medicine.

hydrastis (golden seal, orange root, yellow root, yellow puccoon, turmeric root, Indian turmeric). Dried rhizomes and roots of Hydrastis canadensis, containing the alkaloids berberine, canadine and hydrastine; used in medicine.

hydrate. Substance which crystallizes from an aqueous solution with a definite amount of water, *e.g.*, $CuSO_4.5H_2O$.

hydrated complex. Configuration of substance with large quantity of adsorbed water forming an intermediate between a chemical compound and a dispersion.

hydrated hydrogen bromide. $HBr.H_2O$; m.w. 98.94; col. liq.; sp.gr. 1.78.

$HBr.H_2O$ (47.8%); m.w. 98.94; col. liq.; sp.gr. 1.49; m.p. −11; b.p. 126; s.w.; s.al.

$HBr.2H_2O$; m.w. 116.96; wh. cr.; sp.gr. 2.11^{-15}; m.p. −11; s.w.; s.al.

Hydratex clay. Hydrous aluminum silicate; ylsh. powd.; sp.gr. 2.6; used as filler for rubber, for paper coating.

Hydratex-R. Refined clay.

hydration. Action in which water is one of the reactants with the formation of only one product. The introduction of a hydroxyl group.

hydration of ions. Combination of ions in aqueous solution with one or more molecules of water by the formation of co-ordinate links.

Hydratite. Ammonium stearate; used in waterproofing cement.

hydratripic alcohol. 2-methyl-2-phenylethanol.

hydratropic acid (α-methyl-α-toluic acid; α-phenyl propionic acid). $C_6H_5.CH(CH_3)COOH$; m.w. 150.08; col. liq.; m.p. < −20; b.p. 265; sl.s.w.

hydraulic cement. Cement which hardens or sets when immersed in or in contact with water.

hydraulic gradient. Rate of fall of pressure head along a conduit filled with flowing liquid.

hydraulic index. Ratio of amount of silica + alumina × 100 to lime + magnesia in Portland cement.

hydraulic lime. Specially treated lime containing calcium aluminum silicates and hardening under water.

hydraulic modulus. Ratio of lime percentage to sum of percentages of silica, alumina and iron oxide present in a cement.

hydraulic oil. Fluid used for transmitting pressure, possessing inertness, stability, non-corrosiveness and slow change of viscosity with temperature, *e.g.*, special glycerides and esters.

hydraulic radius. Cross-sectional area of flow divided by the wetted perimeter of a cross-section of the conduit.

hydraulics. Hydrodynamics; science of fluids in motion.

hydraulic system. System of power transmission using an incompressible fluid as the power-transmitting medium.

hydrazide. Compound in which the amino group of carbonamides is replaced by the hydrazino group.

hydrazine. $NH_2.NH_2$; m.w. 32.05; col. liq. or wh. cr.; sp.gr. liq. 1.011^{15}; m.p. 1.4; b.p. 113.5; s.w.; s.al.; used as reducing agent.

hydrazine azide. See hydrazine azoimide.

hydrazine azoimide (hydrazine azide). $N_2H_4.HN_3$; m.w. 75.08; deliq.; m.p. 75.4; s.w.; s.al.

hydrazine (bi)tartrate. See hydrazine acid tartrate.

hydrazine chloride. See hydrazine monochloride.

hydrazine dichloride (diamine hydro-

09165b 364

EXHIBIT 3

DORLAND'S ILLUSTRATED

Medical Dictionary

Twenty-sixth Edition

09/656 364

image of a test object seen reflected in a mirror by the sound eye is projected by the other eye to a drawing board, where it is traced with a pencil guided by the hand of the subject.

cheirospasm (ki'ro-spazm) [*cheiro-* + Gr. *spasmos* spasm] spasm of the muscles of the hand.

chelate (ke'lāt) [Gr. *chēlē* claw] to combine with a metal in complexes in which the metal is part of a ring. By extension, a chemical compound in which a metallic ion is sequestered and firmly bound into a ring within the chelating molecule. Chelates are used in chemotherapeutic treatments for metal poisoning.

chelation (ke-la'shun) combination with a metal in complexes in which the metal is part of a ring.

chelen (ke'len) ethyl chloride.

chelicera (ke-lis'er-ah) a pair of pincer-like head appendages of spiders, scorpions, and other arachnids.

Chel-Iron (kēl'i-ron) trademark for preparations of ferrocholinate.

cheloid (ke'loid) keloid.

cheloma (ke-lo'mah) keloid.

chelonian (ke-lo'ne-an) [Gr. *chelōnē* tortoise] pertaining to turtles and tortoises, (order Chelonia).

chemabrasion (kēm-ah-bra'shun) superficial destruction and exfoliation of the epidermis and the upper layer of the dermis by application of a cauterant to the skin; done to remove scars, tattoos, pigmented nevi, etc. Called also *chemexfoliation*. See also *planing*.

chemanesia (kēm"ah-ne'zē-ah) the controlled and reversible amnesia induced by a drug, as in certain anesthesia procedures.

chemasthenia (kem"as-the'ne-ah) an asthenic condition of the chemical processes of the body.

chemexfoliation (kēm'eks-fo'le-a"shun) chemabrasion.

chemiatric (kem"e-at'rik) iatrochemical.

chemiatry (kem'e-ah-tre) [Gr. *chēmeia* chemistry + *iatreia* treatment] iatrochemistry.

chemical (kem'i-kal) 1. of, or pertaining to, chemistry. 2. a substance composed of chemical elements, or obtained by chemical processes.

chemicobiological (kem"i-ko-bi"o-loj'e-kal) biochemical.

chemicocautery (kem"i-ko-kaw'ter-e) chemocautery.

chemicogenesis (kem"i-ko-jen'ē-sis) [*chemistry* + Gr. *genesis* production] development of an ovum by chemical stimulation.

chemicophysical (kem"i-ko-fiz'e-kal) pertaining to chemistry and physics; pertaining to physical chemistry.

chemicophysiologic (kem'i-ko-fiz"e-o-loj'ik) pertaining to physiology and chemistry.

chemiluminescense (kem"i-loo"mi-nes'ens) chemoluminescence.

cheminosis (kem"i-no'sis) [*chemistry* + Gr. *nosos* disease] any disease due to chemical agents.

chemiosmosis (kem"e-os-mo'sis) chemosmosis.

chemiosmotic (kem"e-o-os-mot'ik) chemosmotic.

chemiotaxis (kem"e-o-tak'sis) chemotaxis.

chemiotherapy (kem"e-o-ther'ah-pe) chemotherapy.

chemism (kem'izm) chemical activity; chemical property or relationship.

chemisorption (kem"i-sorp'shun) the chemical adsorption of one material by another, resulting in the production of a different chemical compound.

chemist (kem'ist) 1. an individual skilled in chemistry. 2. (British) a pharmacist.

chemistry (kem'is-tre) [Gr. *chēmeia*] the science that treats of the elements and atomic relations of matter, and of the various compounds of the elements. **analytical c.**, chemistry that deals with analysis of different elements in a compound. **applied c.**, the application of chemistry to industry and the arts; called also *industrial c.* **biological c.**, biochemistry. **colloid c.**, chemistry dealing with the nature and composition of colloids. **dental c.**, the chemistry of materials used in dental procedures and the processes to which they are subjected. **ecological c.**, the study of those chemical compounds synthesized by plants that serve no metabolic purpose but which, by reason of their toxic effect on insects and higher animals, influence a community of interacting plants and animals. **forensic c.**, use of chemical knowledge in the solution of legal problems. **industrial c.**, applied c. **inorganic c.**, that branch of the science of chemistry which deals with compounds that do not occur in the plant or animal worlds; called also *mineral c.* **medical c.**, chemistry as it relates to medicine. **metabolic c.**, biochemistry. **mineral c.**, inorganic c. **organic c.**, that branch of chemistry which deals with compounds that contain carbon. **pharmaceutical c.**, chemistry that deals with the composition and preparation of substances used in treatment of patients or diagnostic studies. **physical c.**, that branch of chemistry which deals with the relationship of chemical and physical properties. **physiological c.**, biochemistry. **structural c.**, chemical study of the structure of molecules. **surface c.**, in the field of catalysis, the study of chemical reactions between the outermost layer of atoms of a solid and molecules brought to the solid surface in the liquid or gaseous state. **synthetic c.**, that branch of chemistry which deals with the building up of chemical compounds from simpler substances or from the elements.

chemo- (ke'mo, kem'o) [Gr. *chēmeia* chemistry] a combining form denoting relationship to chemistry, or to a chemical.

chemoattractant (ke"mo-ah-trak'tant) a chemical (chemotactic) agent that induces an organism or a cell (e.g., a leukocyte) to migrate toward it.

chemoautotroph (ke"mo-aw'to-trōf) a chemoautotrophic microorganism.

chemoautotrophic (kem"o-aw"to-trof'ik) capable of synthesizing cell constituents from carbon dioxide by means of the energy derived from inorganic reactions.

chemobiotic (ke"mo-bi-ot'ik) the combination of a chemotherapeutic agent and an antibiotic, as of one or more of the sulfonamide compounds with penicillin.

chemocautery (ke"mo-kaw'ter-e) destruction of tissue by application of a caustic chemical substance.

chemocephalia (ke"mo-sĕ-fa'le-ah) chamaecephaly.

chemocephaly (ke"mo-sef'ah-le) chamaecephaly.

chemoceptor (ke'mo-sep-tor) chemoreceptor.

chemocoagulation (ke"mo-ko-ag"u-la'shun) coagulation or destruction of neoplasm by the application of chemicals.

chemodectoma (ke"mo-dek-to'mah) [*chemo-* + *dektos* to be received or accepted + *-oma*] any tumor of the chemoreceptor system, such as a tumor of the carotid body, aortic pulmonary bodies, or glomus jugulare; called also *nonchromaffin paraganglioma*.

chemodifferentiation (ke"mo-dif"er-en-she-a'shun) the invisible point of decision which foreruns and controls the actual differentiation of cells into the rudimentary organs of the embryo.

chemodynesis (ke"mo-di'nē-sis) the initiation of cytoplasmic streaming in plant cells by chemicals.

chemoheterotroph (ke"mo-het'er-o-trōf") a microorganism, parasitic or saprophytic, deriving its energy and most of its carbon from the oxidation of preformed organic compounds.

chemoheterotrophic (ke"mo-het"er-o-trōf'ik) pertaining to a chemoheterotroph.

chemohormonal (ke"mo-hor-mo'nal) pertaining to drugs having hormone activity.

chemoimmunology (ke"mo-im-u-nol'o-je) the study of the chemical processes involved in immunity; immunochemistry.

chemokinesis (ke"mo-ki-ne'sis) [*chemo-* + Gr. *kinēsis* motion] increased activity of an organism due to the presence of a chemical substance.

chemokinetic (ke"mo-ki-net'ik) pertaining to or exhibiting chemokinesis.

chemolithotroph (ke"mo-lith'o-trōf) an organism that derives its energy from oxidation of inorganic compounds and its carbon from carbon dioxide.

chemolithotrophic (ke"mo-lith"o-trof'ik) deriving energy from the oxidation of inorganic compounds of iron, nitrogen, sulfur, or hydrogen; said of bacteria.

chemoluminescence (ke"mo-loo"mi-nes'ens) luminescence produced by the direct transformation of chemical energy into light energy.

chemolysis (ke-mol'i-sis) [*chemo-* + Gr. *lysis* solution] chemical decomposition.

chemomorphosis (ke"mo-mor-fo'sis) [*chemo-* + Gr. *morphē* form] change of form due to chemical action.

chemonucleolysis (ke"mo-nu"kle-ol'i-sis) [*chemo-* + *nucleo* nucleus + *lysis*] dissolution of the nucleus pulposus of an intervertebral disk by injection of a chemolytic agent, e.g., the enzyme chymopapain; used especially in the treatment of herniation of a disk.

chemoorganotroph (ke"mo-or'gah-no-trōf") an organism that derives its energy and carbon from organic compounds.

chemoorganotrophic (ke"mo-or"gah-no-trof'ik) deriving energy from the oxidation of organic compounds; said of bacteria.

chemopallidectomy (ke"mo-pal"i-dek'to-me) [*chemo-* + *pallidum* + *ektomē* excision] creation of a lesion of the globus pallidus by destruction of tissue by a chemical agent.

chemopallidothalamectomy (ke"mo-pal"i-do-thal"ah-mek'to-me) creation of a lesion of the globus pallidus and thalamus by a chemical agent.

chemopharmacodynamic (ke"mo-far"mah-ko-di-nam'ik) denoting the relationship between chemical constitution and biologic or pharmacologic activity.

chemophysiology (ke"mo-fiz-i-ol'o-je) biochemistry.

chemoprophylaxis (ke"mo-pro"fi-lak'sis) [*chemo-* + Gr. *prophylax* an advanced guard] use of a chemotherapeutic agent as a means of preventing development of a specific disease. **primary c.**, prophylactic use of a chemotherapeutic agent before

09/654 364

Notice of Allowability	Application No. 09/327,135	Applicant(s) Martino et al
	Examiner Shahnam Sharareh	Group Art Unit 1619

ll claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included erewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed due course.

This communication is responsive to 6/5/2000, 8/25/2000

The allowed claim(s) is/are 1, 3-24, and 31-34

The drawings filed on _____ are acceptable.

Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE REE MONTHSROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in BANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.

Applicant MUST submit NEW FORMAL DRAWINGS

☐ because the originally filed drawings were declared by applicant to be informal.

☐ including changes required by the Notice of Draftsperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. _____.

☐ including changes required by the proposed drawing correction filed on _____, which has been approved by the examiner.

☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal lettter addressed to the Official Draftsperson.

Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

y response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES DE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER d DATE of the NOTICE OF ALLOWANCE should also be included.

achment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Interview Summary, PTO-413

☐ Examiner's Amendment/Comment

☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

☐ Examiner's Statement of Reasons for Allowance

09/656 364

Interview Summary	Application No. 09/327,135	Applicant(s) Martino et al
	Examiner Shahnam Sharareh	Group Art Unit 1619

All participants (applicant, applicant's representative, PTO personnel):

(1) *Shahnam Sharareh* (3) *A. C. Matino, Inventor*

(2) *Bruce Stein, Applicant's Representative* (4)

Date of Interview *Aug 23, 2000*

Type: [X] Telephonic [ ] Personal (copy is given to [ ] applicant [ ] applicant's representative).

Exhibit shown or demonstration conducted: [ ] Yes [X] No. If yes, brief description:

Agreement [X] was reached. [ ] was not reached.

Claim(s) discussed: *all*

Identification of prior art discussed:
prior art of record

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:
A.C Martino discussed that the teachings of prior art does not utilize high concentrations of superdisintegrants in non chewable tablets, because such high concentrations can form a gelatinous mass that hinders the optimal dissolution of the said formulation. accordingly, Examiner considers, the instant high concentrations of superdisintegrants in the claimed delavirdine composition as an unexpected finding. Also Dr. Martino indicated that the addition of binder stabilizes the interactions between near neighbor delavirdine molecules so that drug precipitation does not occur and acceptable blood levels are achieved. Applicant is to submit a supplemental declaration to further define their unexpected findings. Applicant is also to limit the broad claims to delavirdine formulations comprising the preffered binders.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendents which would render the claims allowable is available, a summary thereof must be attached.)

1. [X] It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. [ ] Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

U. S. Patent and Trademark Office
PTO-413 (Rev. 10-95) Interview Summary Paper No. 9

09/656 364

Allowable Subject Matter

1. Claims 1, 3-24, 31-34 are allowed.

2. The following is an examiner's statement of reasons for allowance:

the closest prior art; PDR 52nd edition, page 2287, discloses an oral formulation of delavirdine mesylate has been available under the brand name of Rescriptor ® as of June 7, 1997. Rescriptor ® tablets contain inactive ingredients comprising lactose, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, opadry YS-1-7000-E white and carnauba wax; however, after careful consideration of the declarations filed under 37 C.F.R 1.132 by Alice C. Martino, Examiner takes the position that the prior art does not teach or suggest the instant formulations of delavirdine mesylate because: (a) the use of high concentrations of superdisintegrants as claimed is not suggested or described in the art for preparing non-chewable delavirdine oral dosage forms, (b) the addition of a binder such as hydroxypropyl methylcellulose to the prior art formulation of delavirdine to provide acceptable dissolution rate, and to delay delavirdine precipitation to produce acceptable blood levels when compared to equal doses of delavirdine formulation, is not an obvious modification of the prior art teachings. Examiner also views the "unacceptable blood levels" as those blood levels that do not control the viral load in a manner that produces clinical success when a delavirdine formulation is administered alone. Accordingly, the instant claims are free of art.

09/656 364

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh, PharmD whose telephone number is (703) 306-5400. The examiner can normally be reached on Monday to Friday from 8:30 a.m. to 5:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Diana Dudash can be reached on 703-308-2328. The fax phone number for this Group is 703-308-4556. Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 703-308-1235.

sjs 8/22/2000

DIANA DUDASH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

09/656 364

LIST OF REFERENCES CITED BY APPLICANT (Use several sheets if necessary)	Atty. Docket No. 6107.N CN1	Serial 09/32718
	Applicant A. C. Martino, et al.	
	Filing Date June 7, 1999	Group 1619

U.S. PATENT DOCUMENTS

Examiner Initial		Document Number	Date	Name	Class	Subclass	Filing Date If Appropriate
✓	AA	5,563,142	Oct. 8, 1996	JR Palmer, et al	A61K	31/495	Feb. 22, 1994
✓	AB	5,358,941	Oct. 25, 1994	SR Bechard, et al.	A61K	31/66	Dec. 2, 1992
✓	AC	5,225,197	July 6, 1993	IJ Bolt, et al.	A61K	9/68	Apr. 27, 1990
✓	AD	4,810,775	Mar. 7, 1989	Dieter Bendix, et al	C08F	6/12	Mar. 18, 1988
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		Document Number	Date	Country	Class	Subclass	Translation	
							Yes	No
✓	AJ	WO 95/28398	Oct. 26, 1995	WIPO	C07D	401/12	X	
	AK	~~EP 283925~~ (See US 4,810,775, above)						
✓	AL	EP 0 319 074	June 7, 1989	Europe	A61K	31/65	X	
	AM	EP 0 384 600 A	Aug. 29, 1990	Europe	A61K	31/60	X	
✓	AN	WO 98/01114	Jan. 15, 1998	WIPO	A61K	9/16	X	

OTHER PRIOR ART (Including Author, Title, Date, Pertinent Pages, Etc.)

✓	AO	International Journal of Pharmaceutics, 154, 59-66 (1997) Inhibitory effects of water-soluble polymers on precipitation of RS-8359
✓	AP	JP 84-185584 (Abstract only - published as JG 1063-61A), April 4, 1994 Japan
✓	AQ	Chemical Abstracts, vol. 126, no. 11, 17 March 1997 abstract no. 139440
✓	AR	Antimicrob. Agents Chemother. (1997), 41(1), 169-174, 1997
	AS	
	AT	

Form 1449
1/92-bis

09/656 364

LIST OF REFERENCES CITED BY APPLICANT *(Use several sheets if necessary)*	Atty. Docket No. 6107.N CN1	Serial [redacted] 09/327185
	Applicant A. C. Martino, et al.	
	Filing Date June 7, 1999	Group
AV		
Examiner	Date Considered 8/22/2002	

OIPE JC46 FEB 25 2000 PATENT & TRADEMARK OFFICE

Form 1449
1/92-ka